

359889

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
2 August 2001 (02.08.2001)

PCT

(10) International Publication Number  
**WO 01/54667 A1**

- (51) International Patent Classification<sup>7</sup>: **A61K 9/14**
- (21) International Application Number: **PCT/US01/02399**
- (22) International Filing Date: **25 January 2001 (25.01.2001)**
- (25) Filing Language: **English**
- (26) Publication Language: **English**
- (30) Priority Data:  
**60/178,682**      **28 January 2000 (28.01.2000)**      **US**
- (71) Applicant (*for all designated States except US*):  
**SMITHKLINE BEECHAM CORPORATION**  
[US/US]; One Franklin Plaza, Philadelphia, PA 19103 (US).
- (74) Agents: **DINNER, Dara, L. et al.**; SmithKline Beecham Corporation, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).
- (81) Designated States (*national*): **AE, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CZ, DZ, EE, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, MZ, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, TZ, UA, US, UZ, VN, YU, ZA.**
- (84) Designated States (*regional*): **ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).**
- Published:  
— *with international search report*
- (72) Inventors; and  
(75) Inventors/Applicants (*for US only*): **IGNATIUS, Francis** [IN/US]; 2 Lindenwood Drive, Exton, PA 19341 (US). **BALDONI, John, M.** [US/US]; 20 Rosemary Lane, Glenmoore, PA 19343 (US).
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*



**WO 01/54667 A1**

(54) Title: **ELECTROSPUN PHARMACEUTICAL COMPOSITIONS**

(57) Abstract: The present invention is directed to an electrospun pharmaceutical composition comprising a pharmaceutically acceptable active agent, and a pharmaceutically acceptable polymeric carrier for use in therapy.

## 5 ELECTROSPUN PHARMACEUTICAL COMPOSITIONS

### *FIELD OF THE INVENTION*

This invention relates to nanofibers of drug particles, method of preparation thereof and pharmaceutical compositions containing these nanofibers. This invention  
10 further relates to the use of such nanofibers in designing various dosage forms to achieve maximum bioavailability of a drug moiety.

### *BACKGROUND OF THE INVENTION*

It is known that the rate of dissolution of a particulate drug can increase with  
15 increasing surface area, i.e., decreasing particle size. Consequently, methods of making finely divided drugs have been studied and efforts have been made to control the size and size range of drug particles in pharmaceutical compositions. For example, dry milling techniques have been used to reduce particle size and hence influence drug absorption. However, in conventional dry milling, as discussed by  
20 Lachman, et al., The Theory and Practice of Industrial Pharmacy, Chapter 2, "Milling", p. 45, (1986), the limit of fineness is reached in the region of 100 microns (100,000 nm) when material cakes on the milling chamber. Lachman, et al. note that wet grinding is beneficial in further reducing particle size, but that flocculation restricts the lower particle size limit to approximately 10 microns (10,000 nm).  
25 However, there tends to be a bias in the pharmaceutical art against wet milling due to concerns associated with contamination. Commercial airjet milling techniques have provided particles ranging in average particle size from as low as about 1 to 50 micrometers (1,000-50,000 nm).

30 Other techniques for preparing pharmaceutical compositions include loading drugs into liposomes or polymers, e.g., during emulsion polymerization. However, such techniques have problems and limitations. For example, a lipid soluble drug is often required in preparing suitable liposomes. Further, unacceptably large amounts of the liposome or polymer are often required to prepare unit drug doses. Further still,  
35 techniques for preparing such pharmaceutical compositions tend to be complex. A principal technical difficulty encountered with emulsion polymerization is the

removal of contaminants, such as unreacted monomer or initiator, which can be toxic, at the end of the manufacturing process.

5 U.S. Pat. No. 4,540,602 (Motoyama et al.) discloses a solid drug pulverized in an aqueous solution of a water-soluble high molecular substance using a wet grinding machine. However, Motoyama et al. teach that as a result of such wet grinding, the drug is formed into finely divided particles ranging from 0.5 .mu.m (500 nm) or less to 5 .mu.m (5,000 nm) in diameter.

10 US Patent No. 5,145,684 (Liversidge et al) discloses dispersible crystalline drug substances having particle sizes lower than 400nm, for increased bioavailability, produced by wet milling.

15 EPO 275,796 describes the production of colloidal dispersible systems comprising a substance in the form of spherical particles smaller than 500 nm. However, the method involves a precipitation effected by mixing a solution of the substance and a miscible non-solvent for the substance and results in the formation of non-crystalline nanoparticle. Furthermore, precipitation techniques for preparing particles tend to provide particles contaminated with solvents. Such solvents are often toxic and can  
20 be very difficult, if not impossible, to adequately remove to pharmaceutically acceptable levels to be practical.

U.S. Pat. No. 4,107,288 describes particles in the size range from 10 to 1,000 nm containing a biologically or pharmacodynamically active material. However, the  
25 particles comprise a crosslinked matrix of macromolecules having the active material supported on or incorporated into the matrix.

Solid dispersions of drugs in polymers are being investigated to address the diminished bioavailability of poorly water soluble drugs. For a recent review see  
30 Serajuddin, Journal of Pharmaceutical sciences, 1999, 88(10), 1058.

An area of great interest is the rapid dissolve dosage forms, which is targeted towards the specific needs of pediatric, geriatrics and patients with dysphagia.

35 U.S. Pat. No. 4,855,326 describes a melt spinnable carrier agent such as sugar is combined with a medicament then converted into fiber form by melt spinning with "cotton candy" fabricating equipment. The as-spun product is converted to

compacted individual dosage units. For certain medicaments a binding agent is added to the carrier agent. Examples are presented for oral administration, topical application, systemic and non-systemic, intravenous and intra-muscular infusion via multicameral containers. All applications utilize the extraordinarily rapid entry into  
5 solution upon contact with a solvent.

U.S. Pat. Nos. 4,946,684; 5,298,261; 5,466,464; 5,501,861; 5,762,961; 5,866,163 disclose taste masked rapidly dissolving dosage forms having organoleptically acceptable properties disintegrate rapidly in patients mouth without chewing or with  
10 minimum amount of water.

U.S. Pat. No. 5,948,430 discloses a polymeric film composition providing instant wettability followed by rapid dissolution/disintegration upon administration in the oral cavity. This may be applicable only to soluble drugs.  
15

Pulmonary delivery, both as immediate and modified release, dosage forms are being actively investigated.

U.S. Pat. No. 5,747,001 discloses the advantages of aerosolized nanoparticles in  
20 pulmonary delivery.

WO 99/48476 describes the use of drug/carrier particles having elongation ratio greater than 1.6 for improved delivery by inhalation. Such particles are either produced by SCF technique or by a complex precipitation process. Electrospinning  
25 provides a direct, scalable process for the production of nanoparticles having greater elongation ratios.

US 5, 985,309 discloses large porous biodegradable microspheres containing proteins and peptides for pulmonary delivery.  
30

It would be desirable to design a simple pharmaceutical composition which provides for all the positive attributes of the above dosage forms by combining the enhanced bioavailability of nanoparticles and physico-chemical characteristics of a nanofiber in a polymeric carrier matrix, in which the drug nanoparticles are homogeneously  
35 embedded, such that a convenient dosage form such as a rapid dissolve, immediate, delayed, modified release could be produced by simply selecting the appropriate polymer, without having to change the process.

### *SUMMARY OF THE INVENTION*

One object of the present invention is a process for electrospinning a pharmaceutically acceptable active agent, or agents, in the presence of a high molecular weight polymeric carrier that acts as viscosity enhancer and fiber forming agent. The process of making the electrospun pharmaceutical composition may be from a solution or a melt.

The present invention is also directed to a pharmaceutical composition comprising an electrospun fiber of a pharmaceutically acceptable polymeric carrier integrated with a pharmaceutically acceptable active agent.

The present invention is also directed to use of an electrospun pharmaceutical composition comprising a pharmaceutically acceptable active agent, and a pharmaceutically acceptable polymeric carrier directly for oral administration, pulmonary administration, or for dissolution into a liquid media for administration, such as a suspension or solution or by parenteral/intramuscular or intracavernosum injection.

### *BRIEF DESCRIPTION OF THE DRAWINGS*

Figure 1 demonstrates electrospinning of viscous drug/polymer compositions either in solution or in melt form to produce nanofibers.

Figure 2 shows the dissolution rate of nanofibers containing nabumetone normalized with respect to nanoparticles of nabumetone.

Figure 3 shows a scanning electron microscope (SEM) of 60% w/w nabumetone spun with POLYOX® fibers.

### *DETAILED DESCRIPTION OF THE INVENTION*

The present invention is directed to a novel composition of an electrospun fiber which fiber is the result of a high molecular weight polymeric carrier that acts as viscosity enhancer and fiber forming agent, and which carrier is spun with a pharmaceutically acceptable agent or drug.

As used herein the term "integrated" means that the drug is integrated with, admixed with, comingled with, or intermixed with the carrier. It is not coated on the surface of an electrospun fiber (woven or non-woven). Specifically the fiber contains both the agent and the carrier together, preferably in a homogeneous manner. While it is

recognized that incomplete stirring of the solutions or the neat/melted compositions may result in some heterogeneity of the resultant fiber, the premise is that the drug and the carrier are spun together, rather than being applied in a later step to a fiber.

- 5 The electrospun fibers of the present invention are expected to have diameters in the nanometer range, and hence provide a very large surface area. The process generates fibers where a high surface to volume ratio is important. This extremely high surface area has profound influence on the bioavailability of a poorly water soluble drug, since it is known that increased surface can lead to increased dissolution rate.

10

A suitable dosage form, such as oral or parenteral form, including pulmonary administration, may be designed by judicious consideration of polymeric carriers, in terms of their physico-chemical properties as well as their regulatory status. Other pharmaceutically acceptable excipients may be included to ameliorate the

15 stabilization or de-agglomeration of the drug nanoparticles. The pharmaceutical excipients might also have other attributes, such as absorption enhancers.

20

Electrospun pharmaceutical dosage form may be designed to provide rapid dissolution, immediate, delayed, or modified dissolution, such as sustained and /or pulsatile release characteristics.

25

Taste masking of the active agent can also be achieved by using polymers having functional groups capable of promoting specific interactions with the drug moiety. The electrospun dosage forms may be presented as compressed tablets, sachets or

films. Conventional dosage forms such as immediate, delayed and modified release systems can be designed by appropriate choice of the polymeric carrier, drug combination, as described in the art.

30

It is one object of the present invention to provide pharmaceutically acceptable drug nanoparticles embedded homogeneously in polymeric nanofibers, such that the drug readily bioavailable independent of the route of administration.

35

Electrospinning, commonly referred to as electrostatic spinning, is a process of producing fibers, with diameters in the range of 100nm. The process consists of applying a high voltage to a polymer solution or melt to produce a polymer jet. As the jet travels in air, the jet is elongated under repulsive electrostatic force to produce nanofibers. The process has been described in the literature since the 1930. A

variety of polymers both natural and synthetic having optimal characteristics have been electrospun under appropriate conditions to produce nanofibers, (see Reneker et al., Nanotechnology, 1996, 7, 216). Different applications have been suggested for these electrospun nanofibers, such as air filters, molecular composites, vascular  
5 grafts, and wound dressings.

U.S. Patent No. 4,043,331, is intended for use as a wound dressing whereas U.S. Patent No. 4,044,404, and US Patent No. 4,878,908 are tailored towards creating a blood compatible lining for a prosthetic device. All of the disclosed water insoluble  
10 polymers are not pharmaceutically acceptable for use herein, however the water soluble polymers disclosed are believed to be pharmaceutically acceptable. None of the preparations in these patents disclose a working example of an electrospun fiber with an active agent. The patents claim the use of enzymes, drugs and/or active carbon on the surface of the nanofibers, prepared by immobilizing the active  
15 moieties so that they act at the site of application and "do not percolate throughout the body".

EP 542514, US 5,311,884 and US 5,522,879 pertain to use of spun fibers for a piezoelectric biomedical device. The piezoelectric properties of fluorinated  
20 polymers, such as those derived from a copolymer of vinylidene fluoride and tetrafluoroethylene are not considered pharmaceutically acceptable polymers for use herein.

US Patent 5,024,671 uses the electrospun porous fibers as a vascular graft material which is filled with a drug in order to achieve a direct delivery of the drug to the  
25 suture site. The porous graft material is impregnated (not electrospun) with the drug and a biodegradable polymer is added to modulate the drug release. The vascular grafts are also made from non-pharmaceutically acceptable polymers, such as the polytetrafluorethylene or blends thereof.

30 US Patent No. 5,376,116, US Patent No. 5,575,818, US Patent No. 5,632,772, US Patent No. 5,639,278 and US Patent No. 5,724,004 describe one form or another of a prosthetic device having a coating or lining of an electrospun non-pharmaceutically acceptable polymer. The electrospun outer layer is post-treated with a drug such as  
35 disclosed in the '116 patent (for breast prosthesis). The other patents describe the same technology and polymers but apply the technique to other applications, such as endoluminal grafts or endovascular stents.

Consequently, the present invention is the first to produce a pharmaceutical composition of an active agent(s) and a pharmaceutically acceptable polymer as an electrospun fiber. The homogenous nature of this process produces a quantity of  
5 fibers which allow for nanoparticles of drugs to be dispersed throughout. The size of particle, and quality of dispersion provide for a high surface area of drug. One use of the increased surface area of drug is improved bioavailability in the case of a poorly water soluble drug. Other uses would be for decreased drug-drug or enzymatic interactions.

10 The present invention is therefore directed to use in any form of a nanofibrous drug either alone, or in combination with a pharmaceutically acceptable polymer (or combination thereof) for enhancing the bioavailability of a drug, preferably a poorly water soluble drug.

15 The present invention is also directed to a rapidly dissolving dosage form comprising an electrospun water soluble polymer in combination with an active agent, such that the rapid dissolving dosage form disintegrates in a rapid manner, over a short time period, in the mouth or other suitable body cavity. In the oral context this would  
20 produce small particulate matter, which could be ingested without needing water.

A rapid dissolve dosage form may include a drug which is either water soluble or water insoluble. A rapid onset of action is a not prerequisite for a rapid dissolve dosage form. For a bitter tasting drug it may be advantageous to have it in an  
25 insoluble form, either by its own solubility characteristics or by polymer coating. Therefore, the main attribute of a rapid dissolve dosage form is that the excipients rapidly disintegrate in the mouth, exposing the drug particles to be easily swallowed. This being the case, electrospun polymer (water-soluble) nanofibers may suitably be premixed with drug during spinning or post mixed during fabrication of the rapid  
30 dissolve dosage form.

While the application of this process may be of use for incorporation of a pharmaceutically acceptable drug for topical delivery, it is primarily oriented towards oral, intravenous, intramuscular, or inhalation usage.

35 Pharmaceutically acceptable agents, actives or drugs as used herein, is meant to include active agents having a pharmacological activity for use in a mammal,



preferably a human. The pharmacological activity may be prophylactic or for treatment of a disease state. The usage is not meant to include agricultural or insecticide usage for application to plants or soil. Use of the electrospun fiber as a woven or non-woven fabric for direct application as a topical treatment in wound dressing or in clothing is also not an aspect of the present invention. However, use of the fibers in a pharmaceutical formulation for topical administration are considered within the scope of the present invention.

As used herein the term's "active agent", "drug moiety" or "drug" are used interchangeably.

Water solubility of the active agent is defined by the United States Pharmacopeia. Therefore, active agents which meet the criteria of very soluble, freely soluble, soluble and sparingly soluble as defined therein are encompassed this invention. It is believed that the electrospun polymeric composition which most benefit those drugs which are insoluble or sparingly soluble.

Suitable drug substances can be selected from a variety of known classes of drugs including, for example, analgesics, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics (including penicillin's), anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytic sedatives (hypnotics and neuroleptics), astringents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, corticosteroids, cough suppressants (expectorants and mucolytics), diagnostic agents, diuretics, dopaminergics (antiparkinsonian agents), haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radiopharmaceuticals, sex hormones (including steroids), anti-allergic agents, stimulants and anorexics, sympathomimetics, thyroid agents, PDE IV inhibitors, NK3 inhibitors, CSBP/RK/p38 inhibitors, antipsychotics, vasodilators and xanthines.

Preferred drug substances include those intended for oral administration and intravenous administration. A description of these classes of drugs and a listing of species within each class can be found in Martindale, The Extra Pharmacopoeia, Twenty-ninth Edition, The Pharmaceutical Press, London, 1989, the disclosure of

which is hereby incorporated herein by reference in its entirety. The drug substances are commercially available and/or can be prepared by techniques known in the art.

As noted, the electrospun composition may also be able to taste mask the many bitter  
5 or unpleasant tasting drugs, regardless of their solubility. Suitable active ingredients for incorporation into fibers of the present invention include the many bitter or unpleasant tasting drugs including but not limited to the histamine H<sub>2</sub>-antagonists, such as, cimetidine, ranitidine, famotidine, nizatidine, etinidine; lupitidine, nifenidine, niperotidine, roxatidine, sulfotidine, tuvatidine and zaltidine; antibiotics,  
10 such as penicillin, ampicillin, amoxycillin, and erythromycin; acetaminophen; aspirin; caffeine, dextromethorphan, diphenhydramine, bromopheniramine, chloropheniramine, theophylline, spironolactone, NSAIDS's such as ibuprofen, ketoprofen, naprosyn, and nabumetone; 5HT<sub>3</sub> inhibitors, such as granisetron (Kytril®), or ondansetron (Zofran®); serotonin re-uptake inhibitors, such as  
15 paroxetine, fluoxetine, fluvoxamine, and sertraline; vitamins such as ascorbic acid, vitamin A, and vitamin D; dietary minerals and nutrients, such as calcium carbonate, calcium lactate, etc., or combinations thereof.

Suitably, the above noted active agents, in particular the anti-inflammatory agents,  
20 may also be combined with other active therapeutic agents, such as various steroids, decongestants, antihistamines, etc., as may be appropriate.

Preferably, the active agent is nabumetone, cis-4-Cyano-4-[3-cyclopentyloxy]-4-methoxyphenyl]cyclohexanecarboxylic acid, ASA, paroxetine (Seroxat®), Ariflo,  
25 ropirinole (Requip®), rosiglitazone (Avandia®), or hydrochlorothiazide and traimeterene (Dyazide®).

Other suitable active agents are amprenavir (Agenerase®), lamivudine (Epivir®), epoprostenol (Flolan®), zanamivir (Relenza®), alosetron (Lotronex®),  
30 alclometasone (Aclovate®), beclomethasone (Beclovent® and Beconase®), malphalan (Aleran®), naratriptan (Amerge®), succinylcholine, cefuroxime (Ceftin®), ceftazidime (Ceptaz®), cefuroxime (Zinacef®), zidovudine (Retrovir®), fluticasone (Flonase® or Cutivate®), pyrimethamine (Daraprim®), colfosceril, sumatriptan (Imitrex®), lamotrigine (Lamictal®), chlorambucil (Leukeran®),  
35 atovaquone (Malaron® or Mepron®), mivacurium (Mivacron®), busulfan (Myleran®), vinorelbine (Navelbine®), cisatracurium (Nimbex®), doxacurium (Nuromax®), atacurium (Tracrium®), oxiconazole (Oxistat®), mercaptopurine

(Purinethol®) and thioguanine (Tabloid®), grepafloxacin (Raxar®), salmeterol (Serevent®), clobetasol (Temovate®), ranitidine, famotidine, omeprazole (R and S isomers), remifentanyl (Ultiva®), valacyclovir (Valtrex®), acyclovir (Zovirax®), famciclovir (Famvir®), penciclovir (Denavir®), albuterol (Ventolin®), bupropion (Wellbutrin® or Zyban®), or abacavir (Ziagen®), 4-(3,4-dihydro-1-methyl-2(1H)-isoquinoliny)-N-(4-fluorophenyl)-5,6-dimethyl-2-pyrimidinamine, (N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine); telmisartan, lacidipine, eniluracil, amoxicillin (Amoxcil®), clavulanate, mupirocin, ticarcillin, cerivastatin (Baycol®), carvedilol (Coreg®), topotecan (Hycamtin®), Factive®, Locilex®, Novastan®, Tranilast, Lotrifiban, 8-[(4-Amino-1-methylbutyl)amino]-2,6-dimethoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinoline succinate, (1S,2R,3S)-1-(1,3-Benzodioxol-5-yl)-2,3-dihydro-3-[2-(2-hydroxyethoxy)-4-methoxyphenyl]-5-propoxy-1H-indene-2-carboxylic acid, nelarabine, dutasteride, maribavir, 3-(3-{1-[(Isopropyl-phenyl-carbamoyl)-methyl]-2,4-dioxo-5-phenyl}-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-ureido)-benzoic acid; 6-amino-3-(2,3,5-trichlorophenyl)pyrazin-2-ylamine; (2R,3R,4S,5R)-2-[6-Amino-2-(1S-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-5-(2-ethyl-2H-tetrazol-5-yl)-tetrahydro-furan-3,4-diol; (6 $\alpha$ ,11 $\beta$ ,16 $\alpha$ ,17 $\alpha$ )-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-([[(3S)-2-oxotetrahydrofuran-3-yl]thio]carbonyl)androsta-1,4-dien-17-yl propionate; (3S)-tetrahydrofuran-3-yl (1S,2R)-3-[[[4-aminophenyl)sulfonyl] (isobutyl)amino]-1-benzyl-2-(phosphonoxy)propylcarbamate; (3R,5R)-3-Butyl-3-ethyl-7,8-dimethoxy-5-phenyl-2,3,4,5-tetrahydro-1,4-benzothiazepine 1,1-dioxide; (1S,3S,4S,8R)-3-(3,4-dichlorophenyl)-7-azatricyclo[5.3.0.0<sup>4,8</sup>]decan-5-ol; (2S,3S,5R)-2-(3,5-Difluorophenyl)-3,5-dimethyl-2-morpholinol; (S)-2-(2-Benzoyl-phenylamino)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid; 3'-[(2-{[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino}ethyl)amino] [1,1'-biphenyl]-3-carboxylic acid; (2S)-2-{[(1Z)-1-methyl-3-oxo-3-phenylprop-1-enyl]amino}-3-{4-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]phenyl}propanoic acid; or combinations and mixtures thereof of all compounds noted herein.

30

In short, for use herein, a poorly soluble drug should have good solubility in an organic solvent, or a poorly soluble drug must be useable in a melt process as further described below.

35

The nanofibers of this invention will contain high molecular weight polymeric carriers. These polymers, by virtue of their high molecular weight, form viscous solutions which can produce nanofibers, when subjected to an electrostatic potential.

Suitable polymeric carriers can be preferably selected from known pharmaceutical excipients. The physico-chemical characteristics of these polymers dictate the design of the dosage form, such as rapid dissolve, immediate release, delayed  
5 release, modified release such as sustained release, or controlled release, pulsatile release etc.

DNA fibers have been used to form fibers by electrospinning, Fang et al., J. Macromol. Sci.-Phys., B36(2), 169-173 (1997). Incorporation of a pharmaceutically  
10 acceptable active agent, such as a biological agent, a vaccine, or a peptide, with DNA, RNA or derivatives thereof as a spun fiber is also within the scope of this invention.

The fiber forming characteristics of the polymer are exploited in the fabrication of  
15 nanofibers. Hence, molecular weight of the polymer is the single most important parameter for choice of polymer. As previously noted, a large number of polymers have already been electrospun, such as cellulose acetate, PVA, PEO, PVP, polyacrylamide, polyurethane, polycarbonate, PTFE, PE, PP, polyacrylate, Kevlar, PHB, polyaniline, DNA, poly (phenylene terphthalamide) and silk.

20 However, for purposes herein additional representative examples of polymers suitable for pharmaceutical applications, include, but are not limited to, poly(ethylene oxide), polyvinyl alcohol, polyvinyl acetate, polyvinyl pyrrolidone, hyaluronic acid, alginates, carragenen, cellulose derivatives such as carboxymethyl  
25 cellulose sodium, methyl cellulose, ethylcellulose, hydroxyethyl cellulose, hydroxypropylcellulose, hydroxypropylmethyl cellulose, hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, noncrystalline cellulose, starch and its derivatives such as hydroxyethyl starch, sodium starch glycolate, chitosan and its derivatives, albumen, gelatin, collagen, polyacrylates and its derivatives such as the  
30 Eudragit family of polymers available from Rohm Pharma, poly(alpha-hydroxy acids) and its copolymers such poly(caprolactone), poly(lactide-co-glycolide), poly(alpha-aminoacids) and its copolymers, poly(orthoesters), polyphosphazenes, poly(phosphoesters), and polyanhydrides, or mixtures thereof.

35 Most of these pharmaceutically acceptable polymers are described in detail in the Handbook of Pharmaceutical excipients, published jointly by the American Pharmaceutical association and the Pharmaceutical society of Britain.

Preferably, the polymeric carriers are divided into three categories: (1) water soluble polymers useful for rapid dissolve and immediate release of active agents, (2) water insoluble polymers useful for controlled release of the active agents; and (3) pH sensitive polymers for pulsatile or targeted release of active agents. It is recognized that combinations of both carriers may be used herein. It is also recognized that several of the polyacrylates are pH dependent for the solubility and may fall into both categories.

Water soluble polymers include but are not limited to, poly(ethylene oxide), polyvinyl alcohol, polyvinyl pyrrolidone, hyaluronic acid, alginates, carragenen, cellulose derivatives such as carboxymethyl cellulose sodium, hydroxyethyl cellulose, hydroxypropylcellulose, hydroxypropylmethyl cellulose, hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, starch and its derivatives such as hydroxyethyl starch, sodium starch glycolate, dextrin, chitosan and its derivatives, albumen, zein, gelatin, and collagen.

Preferably, a water soluble polymer for use herein is polyethylene oxide, such as the brand name POLYOX®. It is recognized that the polymers may be used in varying molecular weights, with combinations of molecular weights for one polymer being used, such as 100K, 200K, 300K, 400K, 900K and 2000K. Sentry POLYOX is a water soluble resin which is listed in the NF and have approximate molecular weights from 100K to 900K and 1000K to 7000K. These commercially available polymers may be used as 1%, 2% and 5% solutions (depending upon molecular weight).

NF grades of Sentry POLYOX, a water soluble resin is available with varying molecular weights as noted above. A table, shown below, provides further information on the grade vs. approx. molecular weight for use in the examples herein.

Viscosity range at 25 °C, cP				
NF Grade	Approximate mol. weight	5% solution	2% solution	1% solution
WSRN-10	100,000	30-50		
WSRN-80L	200,000	500		
WSRN-80H	200,000	90-105		
WSRN-750	300,000	500-1200		
WSRN-3000	400,000	1,250-4,500		
WSR-20S	600,000	4,500-8,800		
WSR-1105	900,000	8,800-17,600		
WSRN-12K	1,000,000		400-800	
WSRN-60K	2,000,000		2,000-4,000	
WSR-301	4,000,000			1,500-4,500
WSR coagulant	5,000,000			4,500-7,500
WSR-303	7,000,000			7,500-10,000

Additional preferred polymers include povidone, having K values and molecular weight ranges from :

K value	Mol. wt.
12	25
15	8000
17	10,000
25	30,000
30	50,000
60	400K
90	1000K
120	3000K

- 5 Water insoluble polymers include but are not limited to, polyvinyl acetate, methyl cellulose, ethylcellulose, noncrystalline cellulose, polyacrylates and its derivatives such as the Eudragit family of polymers available from Rohm Pharma (Germany), poly(alpha-hydroxy acids) and its copolymers such as poly(ε-caprolactone), poly(lactide-co-glycolide), poly(alpha-aminoacids) and its copolymers,
- 10 poly(orthoesters), polyphosphazenes, poly(phosphoesters), and polyanhydrides.

These pharmaceutically acceptable polymers and their derivatives are commercially available and/or be prepared by techniques known in the art. By derivatives it is meant, polymers of varying molecular weight, modification of functional groups of the polymers, or co-polymers of these agents, or mixtures thereof.

5

Further, two or more polymers can be used in combination to form the fibers as noted herein. Such combination may enhance fiber formation or achieve a desired drug release profile.

- 10 The choice of polymers taken with the active agent may provide suitable taste masking functions for the active agents. For instance, use of an ionic polymer of contrasting charge, such as a cationic polymer complexed with an anionic active agent, or an anionic polymer complexed with a cationic active agent may produce the desired results. Addition of a second taste masking agent, such as a suitable  
15 cyclodextrin, or its derivatives may also be used herein.

- The polymeric composition may be electrospun from a solvent base or neat (as a melt). Solvent choice is preferably based upon the solubility of the active agent. Suitably, water is the best solvent for a water soluble active agent, and a water  
20 soluble polymer like POLYOX. Alternatively, water and a water-miscible organic solvent may used. However, it is necessary to use an organic solvent to prepare a homogenous solution of the drug with polymer when the drug is non-water soluble, or sparingly soluble.

- 25 It is recognized that these polymeric composition which are spun neat may also contain additional additives such as, plasticizers. The plasticizers are employed to assist in the melting characteristics of the composition. Exemplary of plasticizers that may be employed in this invention are triethyl citrate, triacetin, tributyl citrate, acetyl triethyl citrate, acetyl tributyl citrate, dibutyl phthalate, dibutyl sebacate, vinyl  
30 pyrrolidone, propylene glycol, glycol tiracetate, polyethylene glycol, or polyoxyethylene sorbitan monolaurate and combinations or mixtures thereof.

- Preferably, the solvent of choice is a GRASS approved organic solvent, although the solvent may not necessarily be "pharmaceutically acceptable" one, as the resulting  
35 amounts may fall below detectable, or set limits for human consumption they may be used. It is suggested that ICH guidelines be used for selection. GRASS in an acronym for "generally recognized as safe".

Suitable solvents for use herein include, but are not limited to acetic acid, acetone, acetonitrile, methanol, ethanol, propanol, ethyl acetate, propyl acetate, butyl acetate, butanol, N,N dimethyl acetamide, N,N dimethyl formamide, 1-methyl-2-

5 pyrrolidone, dimethyl sulfoxide, diethyl ether, disisopropyl ether, tetrahydrofuran, pentane, hexane, 2-methoxyethanol, formamide, formic acid, hexane, heptane, ethylene glycol, dioxane, 2-ethoxyethanol, trifluoroacetic acid, methyl isopropyl ketone, methyl ethyl ketone, dimethoxy propane, methylene chloride etc., or mixtures thereof.

10

A preferred solvent is a mixture of water and acetonitrile, or water and acetone.

The solvent to polymeric composition ratio is suitable determined by the desired viscosity of the resulting formulation.

15

For electrospinning of a pharmaceutical polymeric composition, key parameters are viscosity, surface tension, and electrical conductivity of the solvent/polymeric composition.

20 By the term "nanoparticulate drug" as used herein, is meant, nanoparticle size of an active agent within the electrospun fiber.

The polymeric carriers may also act as surface modifiers for the nanoparticulate drug. However, a second oligomeric surface modifier may also be added to the electrospinning solution. All of these surface modifiers may physically adsorb to the surface of the drug nanoparticles, so as to prevent them agglomerating.

25

Representative examples of these second oligomeric surface modifier or excipients, include but are not limited to: Pluronics<sup>®</sup> (block copolymers of ethylene oxide and propylene oxide), lecithin, Aerosol OT<sup>™</sup> (sodium dioctyl sulfosuccinate), sodium lauryl sulfate, polyoxyethylene sorbitan fatty acid esters, i.e., the polysorbates such as Tween<sup>™</sup>, such as Tween 20, 60 & 80, the sorbitan fatty acid esters, i.e., sorbitan monolaurate, monooleate, monopalmitate, monostearate, etc. such as Span<sup>™</sup> or Arlacel<sup>™</sup>, Emsorb<sup>™</sup>, Capmul<sup>™</sup>, or Sorbester<sup>™</sup>, Triton X-200, polyethylene glycols, glyceryl monostearate, Vitamin E-TPGS<sup>™</sup> (d-alpha-tocopheryl polyethylene glycol 1000 succinate), sucrose fatty acid esters, such as sucrose stearate, sucrose oleate, sucrose palmitate, sucrose laurate, and sucrose acetate butyrate, etc.

35



Surfactants are added on a weight/weight basis to the drug composition. Suitably, the surfactants are added in amounts of about 10%, preferably about 5% or less. Surfactants can lower the viscosity and surface tension of the formulation, and in  
5 higher amounts can adversely effect the quality of the electrospun fibers.

The surfactant selection may be guided by HLB values but is not necessarily a useful criteria. While HLB surfactants have been utilized herein, such as Tween™ 80 (HLB=10), Pluronic F68 (HLB =28), and SDS (HLB>40), lower HLB value  
10 surfactants, such as Pluronic F92 may also be used.

Another pharmaceutically acceptable excipients may be added to the electrospinning composition. These excipients may be generally classified as absorption enhancers; additional surfactants, flavouring agents, dyes, etc.  
15

Suitable flavoring agents for use herein include, but are not limited to, wintergreen; orange, grapefruit, and cherry-raspberry. While w/w% will vary for each composition, the flavouring agent should be present from about 0.25 to about 5% w/w of the total formulation.  
20

Suitable coloring agents, pigments, or dyes, such as FD&C or D&C approved lakes and dyes, iron oxide and titanium dioxide may also be included in the formulations. The amount of pigment present may be from about 0.1% to about 2.0% by weight of the composition.  
25

Additionally, the formulation may also contain sweeteners such as various natural sugars, aspartame, sodium cyclamate and sodium saccharinate; as well as the flavorants such as those noted above.

30 The polymeric carriers or the second oligomeric surface modifiers, if appropriately chosen, may themselves act as absorption enhancers, depending on the drug. Suitable absorption enhancers for use herein, include but are not limited to, chitosan, lecithin, lectins, sucrose fatty acid esters such as the ones derived from stearic acid, oleic acid, palmitic acid, lauric acid, and Vitamin E-TPGS.

35 Use of the electrospun composition herein may be by conventional capsule or tablet fill. Alternatively, the fibers may be ground, suitably by cryogenic means, for

compression into a tablet or capsule, for use by inhalation, or parenteral administration. The fibers may also be dispersed into an aqueous solution which may then be directly administered by inhaled or given orally. The fibers may also be cut and processed as a sheet for further administration with agents to form a  
5 polymeric film, which may be quick-dissolving.

Another aspect of the present invention is an alternative electrospinning process for making the pharmaceutical compositions described herein. The working examples herein electrostatically charge the solution whereas the pharmaceutical composition  
10 may also be ejected from a sprayer onto a receiving surface which is electrostatically charged and placed at an appropriate distance from the sprayer. As the ejectant travels in the air from the sprayer towards the charged collector, fibers are formed. The collectors can be either a metal screen, or in the form of a moving belt. The fibers may be deposited on a moving belt which could be continuously removed and  
15 taken away for further processing as desired.

In a preferred embodiment of the invention for water insoluble agents, is the active nabumetone, electrospun in w/w% ranges from 0 to 82 %, with 200K, 400K, 900K and 2000K POLYOX, and Tween 80, SDS, Pluronic F68, or TPGS. A preferred  
20 solvent system is water/acetonitrile.

### EXAMPLES

The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the  
25 present invention. All temperatures are given in degrees centigrade, all solvents are highest available purity unless otherwise indicated.

#### Example 1

##### Electrospinning of 25% (w/w) Aspirin composition

30 A stock solution of 2.5% solution of POLYOX WSR N-60K™ (Union Carbide) was prepared in MilliQ™ water by gentle mixing in a shaking water bath. 10 milliliters (hereinafter "mL" or "ml") of this POLYOX solution was added to a solution of 0.12 grams (hereinafter "g") Acetylsalicylic acid (Sigma) in 0.5 mL acetone. The  
35 contents were thoroughly mixed and 1mL of acetone was added to obtain a clear solution. This solution was transferred to a 25mL glass vessel having a 0.03millimeter (hereinafter "mm") capillary outlet at the bottom and two inlets, one

for applying a positive Helium (He) pressure and the other for introducing the electrode. The electrode was connected to the positive terminal of a high voltage power supply (Model D-ES30P/M692, Gamma High Voltage Research Inc. FL). The ground from the high voltage power supply was connected to a rotating drum covered with aluminum foil. The inlet Helium pressure was at 2.5psi and a voltage of +14.5KV was applied to the solution. The dry fibers were collected on a drum rotating a speed of 50-60 rpm. The fibers were peeled off the drum.

The electrospinning process is further described in J. Doshi's Dissertation, of "The ElectroSpinning Process and Applications of Electrospun Fibers", August 1994, University of Akron, which is incorporated herein by reference in its entirety.

#### Example 2

##### Electrospinning of 25% Nabumetone composition

A stock solution of 30% Polyethylene oxide (Molecular weight 400K, Aldrich) was prepared in MilliQ™ water by gentle shaking. 5mL of this 30% solution was added to 0.5g nabumetone (SB Corporation) dissolved in 6ml of acetonitrile. The contents were gently stirred and another 5mL acetonitrile was added in small portions until a clear solution was obtained. 0.1ml of Tween™ 80 (Sigma) was added to the solution. This solution was electrospun using the same conditions described above in Example 1. Fibers were collected and removed from the drum.

#### Example 3

##### Electrospinning of 30% Nabumetone composition

A stock solution of 7.5% (w/v) POLYOX® WSR N-3000 (Molecular weight of approx. 400K, Union Carbide) in MilliQ™ water/acetonitrile was prepared by mixing 15g of PEO in 50ml water and 150mL acetonitrile.

To 10mL of this solution was added 0.4g nabumetone along with 1mL acetonitrile and 0.2mL Tween™ 80 to obtain a homogeneous solution. This solution was electrospun under the same conditions as described above in example 1 to yield 1.3g fibers.

## Example 4

## Electrospinning of 50% Nabumetone composition

To 10mL of the stock solution of water/acetonitrile from Example 3 above was  
5 added 0.8g nabumetone. The solution was homogenized by adding 1mL acetonitrile  
along with 0.2mL Tween™ 80. The solution was spun using similar conditions to  
Example 1 above, but using a feed pressure of 2psi and 16KV to yield 1.2g of fibers.

## Example 5

## 10 Electrospinning of 70% Nabumetone composition

To 5mL of the POLYOX® N-3000 solution from Example 3 was added 0.86g of  
nabumetone. The solution was made homogeneous by adding 1.6mL of acetonitrile  
along with 0.1mL Tween™ 80. The solution was spun using similar conditions to  
15 Example 1 above, but using a feed pressure of 0.5psi and 16KV to yield 0.93g of  
fibers.

## Example 6

## 20 Electrospinning of 80% Nabumetone composition

To a mixture of 2g Nabumetone, 0.1g SDS (JT Baker) and 0.4g POLYOX® WSR-  
1105 (900K) was added 1.2 mL MilliQ® water and 10.5 mL acetonitrile. This  
mixture was left in a shaking water bath at 37°C until all solid material dissolves to  
form a viscous solution. The resultant solution was electrospun using conditions  
25 similar to Example 1 above, but using a feed pressure of 2 psi and 18KV to yield  
2.1g of fibers.

## Example 7

## 30 Electrospinning of 80% Nabumetone composition

To a mixture of 2g Nabumetone, 0.05g Pluronic® F68 (BASF) and 0.4g POLYOX®  
WSR-1105 (900K) was added 1 mL MilliQ® water and 12 mL acetonitrile. This  
mixture was left in a shaking water bath at 37°C until all solid material dissolves to  
form a viscous solution. The resultant solution was electrospun using conditions  
35 similar to Example 1 above, but using a feed pressure of 2 psi and 18KV to yield  
2.1g of fibers.

## Example 8

## Electrospinning of 80% Nabumetone Composition

Two grams of Nabumetone was dissolved in 11mL of acetonitrile. To the solution  
5 was added 0.1g of Vitamin E-TPGS (Eastman) and 0.4g POLYOX<sup>®</sup> WSR-1105  
(900K). The mixture was left in a shaking water bath at 37°C until all solid material  
dissolves to form a viscous solution. The resultant solution was electrospun using  
conditions similar to Example 1 above, but using a feed pressure of 0.5 psi and  
16KV to yield 2g of fibers.

10

## Example 9

## Determination of Nabumetone content in the nanofiber composition

Accurately weighed out 20 to 50mg (depending on the expected drug content) of a  
15 nanofiber composition, such as described above, into a scintillation vial and  
dissolved it 5mL acetonitrile/water (80/20) mixture. The solution was quantitatively  
transferred to a 50mL volumetric flask using acetonitrile/water (80/20) and made up  
to volume (50mL) using acetonitrile/water as diluent. Three different samples taken  
from different parts of fibrous sheets were prepared to determine the macroscopic  
20 heterogeneity within the fibers.

A standard solution of nabumetone was prepared using accurately weighed sample  
of 20mg nabumetone in a 100mL volumetric flask. The sample was made up using  
acetonitrile/water(80:20) as a diluent. 20uL of this solution was injected in Waters  
25 HPLC system equipped with Waters 550 pumps, 717plus autosampler, and  
Spectroflow 783 UV detector. The data acquisition was carried out through a PE  
Nelson Box and Turbochrom (PE) software. The mobile phase consisted of  
acetonitrile/water/acetic acid in the volume ratio of 44/55/1. The flow rate was  
1.4ml/min and the detection was done at 254nm.

30

	Nabumetone Content (wt. %)		
	Sample #1	sample#2	Sample #3
Example 8	81.2	79.5	81.2
Example 6	82.9	82.8	83.0
Example 5	59	61.2	60.8
Example 4	36	36.9	35
Example 3	30	30.5	29.8

### Example 10

#### Residual Solvent Analysis in the Nabumetone nanofibers

- 5 Residual solvent analysis was carried out at QTI (Whitehouse, NJ) using samples dissolved in DMSO (dimethyl sulfoxide) and quantitated by capillary Gas Chromatography. The results, shown in the Table below demonstrate that all the samples analyzed contained less 100ppm of acetonitrile.

10 Table

	acetonitrile content
Example 5	<100ppm
Example 4	< 100ppm
Example 3	< 100ppm

### Example 11

#### In-Vitro dissolution Assay

15

The equipment used for this procedure is a modified USP4, the major differences being: 1) low volume cell; 2) stirred cell; 3) retaining filters which are adequate at retaining sub micron material. The total run time is 20 minutes. with 2.5mg of drug (weigh proportionally more formulated material).

- 20 **Flow Cell Description:** Swinnex filter assemblies obtained from Millipore, having 0.2 micron Cellulose Nitrate membranes. (Millipore, MA) as internal filters. The internal volume of the cell is approximately 2 mL. A Small PTFE stirrer customized to fit the Swinnex assembly (Radleys Lab Equipment Halfround Spinvane F37136) is used. The dissolution medium is water at a flow rate of 5mL/min. The whole set
- 25 up is placed at a thermostat of 37°C. The drug concentration is measured by passing

the eluent through a UV detector having a flow cell dimension of 10mm. The UV detection is carried out at 284nm.

#### Determination of extent of drug solubility

- 5 The experimentation is designed to evaluate drug dissolution rate. As such it is unlikely with poorly soluble drugs and with water as the dissolution medium that 100% of the drug will dissolve in the 20 minute duration of the test. To determine the extent of drug solubility over this period collect all 100ml of solution that elutes from the dissolution cell. Using a conventional UV spectrophotometer compare this
- 10 solution against a reference solution of 2.5mg of active agent, for instance Nabumetone, dissolved in 50/50 methanol/water. (For Nabumetone this can be prepared by 10 fold dilution of a solution containing 25mg Nabumetone in 100mls of 50/50 methanol/water). A suitable wavelength for comparison is 260nm.

15

#### Example 12

Determination of thermal behavior of nabumetone containing nanofibers.

- Thermal studies on nabumetone nanofibers were performed on a MDSC TA (Wilmington, DE). The samples were heated from 0 to 120°C at 2°C/min at a
- 20 modulation frequency of  $\pm 0.159^\circ\text{C}$  every 30 seconds. The nanofibers containing nabumetone two distinct endotherms at 50°C and 75°C corresponding to the melting of POLYOX and nabumetone respectively, when the nabumetone content is above 30% (wt.), below which only one melting endotherm is visible either due to the
- formation of a eutectic mixture or because the endotherms overlap.

25

	Nabumetone content (wt.%)	Melting of POLYOX °C and $\Delta H$	Melting of Nabumetone °C and $\Delta H$
Example 8	81.2	49.4(22.2 J/g)	75(80J/g)
Example 7	84.4	51.5 (22.4 J/g)	75.3 (82.4J/g)
Example 6	82.9	50.5 (19.6J/g)	75.3 (87.3J/g)
Example 5	60.3	49.2 (87.4 J/g)	69 (86.2J/g)
Example 4	35.9	45.1 (69.1J/g)	59 (7.39J/g)
Example 3	30.1	47 (101J/g)	
Example 2	29.3	48 (94.5J/g)	

## Example 13

Electrospinning of 40% cis-4-Cyano-4-[3-cyclopentyloxy]-4-methoxyphenyl]cyclohexanecarboxylic acid composition

- 5 To 10ml of the POLYOX WSRN-3000 solution from Example 3 was added 0.5g of cis-4-Cyano-4-[3-cyclopentyloxy]-4-methoxyphenyl]cyclohexanecarboxylic acid along with 1mL acetonitrile and 0.1mL Tween™ 80 to obtain a homogeneous solution. This solution was electrospun under the same conditions as described above in Example 1 to yield nanofibers containing the title compound.

10

## Example 14

Electrospinning of (S)-3-Hydroxy-2-phenyl-N-(1-phenylpropyl)-4-quinolinecarboxamide Compositions

- 15 Four Hundred milligrams of (S)-3-Hydroxy-2-phenyl-N-(1-phenylpropyl)-4-quinolinecarboxamide was dissolved in 5mL of tetrahydrofuran (G.T Baker). To this solution 450mg of POLYOX® WSR-1105 (900K) and 50mg Vitamin E-TPGS(Eastman) were added. The mixture was left in a shaking water bath at 37°C until all solid material dissolves to form a viscous solution. The viscosity of the solution was reduced by added 5mL of acetonitrile. The resultant solution was electrospun using conditions similar to Example 1 above, but using a feed pressure of 0.5 psi and 16 KV to yield 0.5g of fibers.

20

## Example 15

- 25 Electrospinning of 4-[2-(Dipropylamino)ethyl]-1,3-dihydro-2H-indol-2-one monohydrochloride

Two hundred milligrams of Ropirinole was dissolved in 15ml of milliQ water. To this solution was added 1g of POLYOX® WSR N3000 NF and 50mg of Tween 80.

- 30 The mixture was left shaking in a water bath at 37 °C until all solid material dissolved to form a clear viscous solution. This solution was electrospun using a conditions similar to Example 1, at a feed pressure of 1 psi and 16 KV to yield 0.8g of the material.

35

## Example 16

Electrospinning of 4-[2-(Dipropylamino)ethyl]-1,3-dihydro-2H-indol-2-one monohydrochloride



Three hundred Fifty milligrams of Ropirinole was dissolved in 15ml of milliQ water. To this solution was added 650mg of POLYOX<sup>®</sup> WSR N3000 NF and 50mg of Tween 80. The mixture was left shaking in a water bath at 37 °C until all solid material dissolved to form a clear viscous solution. This solution was electrospun using a conditions similar to Example 1, at a feed pressure of 1 psi and 16 KV to yield 0.7g of the material.

#### Example 17

##### Electrospinning of Paroxetine

One hundred milligrams of paroxetine was dissolved in 20ml of milliQ water. To this solution was added 800mg of POLYOX<sup>®</sup> WSR N3000 NF and 50mg of Tween 80. The mixture was left shaking in a water bath at 37 °C until all solid material dissolved to form a clear viscous solution. This solution was electrospun using a conditions similar to Example 1, at a feed pressure of 1 psi and 16 KV to yield 0.75g of the material.

#### Example 18

##### Electrospinning of Kytril

Three hundred milligrams of Kytril was dissolved in 15ml of milliQ water. To this solution was added 650mg of POLYOX<sup>®</sup> WSR N3000 NF and 50mg of Tween 80. The mixture was left shaking in a water bath at 37 °C until all solid material dissolved to form a clear viscous solution. This solution was electrospun using a conditions similar to Example 1, at a feed pressure of 1 psi and 16 kV to yield 0.7g of the material.

#### Example 19

Electrospinning of 10% 2,3-Dihydro-5-methyl-N-[6-(2-pyridinylmethoxy)-3-pyridinyl]-6-(trifluoromethyl)-1H-indole-1-carboxamide composition

Eight Hundred and Fifty milligrams of POLYOX<sup>®</sup> WSR-1105 (900K) was dissolved in 20ml acetonitrile by shaking overnight in a water bath at 35°C. This forms a thick viscous solution. 5ml of n-methyl pyrrolidone (NMP) and 50mg of Vitamin E-TPGS(Eastman) were added to the solution and stirred. 100mg of the title compound dissolved in 1ml of NMP was added to the polymer solution. The clear solution

obtained was electrospun under identical conditions to Example 1, to yield 0.5g of the product.

#### Example 20

- 5 Electrospinning of 20% 2,3-Dihydro-5-methyl-N-[6-(2-pyridinylmethoxy)-3-pyridinyl]-6-(trifluoromethyl)-1H-indole-1-carboxamide composition

Seven Hundred and Fifty milligrams of POLYOX<sup>®</sup> WSR-1105 (900K) was dissolved in 20ml acetonitrile by shaking overnight in a water bath at 35°C. This  
10 forms a thick viscous solution. 5ml of n-methyl pyrrolidone (NMP) and 50mg of Vitamin E-TPGS(Eastman) were added to the solution and stirred. 200mg of the title compound dissolved in 1ml of NMP was added to the polymer solution. The clear solution obtained was electrospun under identical conditions to Example 1, to yield  
15 0.7g of the product.

#### Example 21

##### Electrospinning of 68% Nabumetone Composition

Three grams of Nabumetone was dissolved in 20mL of acetonitrile. To the solution  
20 was added 0.25g of Vitamin E-TPGS(Eastman), 0.8g POLYOX WSR-1105 (900K) and 0.25g Tween 80. The mixture was left in a shaking water bath at 37°C until all solid material dissolves to form a viscous solution. The resultant solution was electrospun using conditions similar to Example 1 above, but using a feed pressure of 0.5 psi and 16KV to yield 3.5g of fibers.

25 All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

30 The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding  
35 description, utilize the present invention to its fullest extent. Therefore, the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

## What is Claimed Is:

1. A pharmaceutical composition comprising an electrospun fiber of a pharmaceutically acceptable polymeric carrier integrated with a pharmaceutically acceptable active agent.  
5
2. The composition according to Claim 1 wherein the active agent is nanoparticle in size.
- 10 3. The composition according to Claim 1 or 2 wherein the active agent is water soluble.
4. The composition according to Claim 1 or 2 wherein the active agent is water insoluble.  
15
5. The composition according to Claim 1 wherein the active agent is sparingly water soluble.
6. The composition according to Claim 1 or 2 wherein the polymeric carrier is water soluble.  
20
7. The composition according to Claim 1 or 2 wherein the polymeric carrier is water insoluble.
- 25 8. The composition according to Claim 1 wherein the composition further comprises a surfactant which is a block copolymer of ethylene oxide and propylene oxide, lecithin, sodium dioctyl sulfosuccinate, sodium lauryl sulfate, Tween 20, 60 & 80, Span <sup>TM</sup>, Arlacel<sup>TM</sup>, TritonX-200, polyethylene glycol, glyceryl monostearate, d-alpha-tocopheryl polyethylene glycol 1000 succinate, sucrose fatty acid ester, such  
30 as sucrose stearate, sucrose oleate, sucrose palmitate, sucrose laurate, sucrose acetate butyrate, or a mixture thereof.
9. The composition according to Claim 1 or 8 wherein the composition further comprises an absorption enhancer.  
35
10. The composition according to Claim 1 which provides a taste masking effect of the active agent.

11. The composition according to Claim 6 wherein the polymeric carrier is poly(ethylene oxide), polyvinyl alcohol, polyvinyl pyrrolidone, hyaluronic acid, alginates, carragenen, carboxymethyl cellulose sodium, hydroxyethyl cellulose, hydroxypropylcellulose, hydroxypropylmethyl cellulose, hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, starch, hydroxyethyl starch, sodium starch glycolate, chitosan and its derivatives, albumen, gelatin, or collagen.
12. The composition according to Claim 1 wherein the polymeric carrier is polyvinyl acetate, methyl cellulose, ethylcellulose, noncrystalline cellulose, polyacrylates and its derivatives, poly(alpha-hydroxy acids) and its copolymers such poly(caprolactone), poly(lactide-co-glycolide), poly(alpha-aminoacids) and its copolymers, poly(orthoesters), polyphosphazenes, poly(phosphoesters), or polyanhydrides.
13. The composition according to Claim 1 wherein said drug substance is an analgesic, anti-inflammatory agent, anthelmintic, anti-arrhythmic agent, an antibiotic, anticoagulant, antidepressant, antidiabetic agent, antiepileptic, antihistamine, antihypertensive agent, antimuscarinic agent, antimycobacterial agent, antineoplastic agent, immunosuppressant, antithyroid agent, antiviral agent, anxiolytic sedative, astringent, beta-adrenoceptor blocking agent, contrast media, corticosteroid, cough suppressant, diuretic, dopaminergic, homeostatic, immunological agent, lipid regulating agent, muscle relaxant, parasympathomimetic, parathyroid, calcitonin, prostaglandin, radio-pharmaceutical, sex hormone, steroid, anti-allergic agent, antihistaminic, stimulant, sympathomimetic, thyroid agent, vasodilator, PDE IV inhibitor, or a mixture thereof.
14. The composition according to claim 13 wherein the drug substance is an anti-inflammatory agent or a PDE IV inhibitor.
15. The composition according to claim 14 wherein the said active is nabumetone, aspirin, cis-4-Cyano-4-[3-cyclopentyloxy]-4-methoxyphenyl]-cyclohexanecarboxylic acid, or (S)-3-Hydroxy-2-phenyl-N-(1-phenylpropyl)-4-quinolinecarboxamide.
16. The composition according to Claim 13 wherein the active agent is Ropirinole, Paroxetine, or Kytril.

17. The composition according to Claim 1 which is intended for oral administration.
- 5 18. The composition according to Claim 1 in which the active agent demonstrates improved bioavailability.
19. The composition according to Claim 1 in which the electrospun fiber is encapsulated or compressed into a tablet.
- 10 20. The composition according to Claim 1 in which the electrospun fiber is further ground.
21. The composition according to Claim 1 which results in a rapid dissolution of the fiber.
- 15 22. The composition according to Claim 1 which results in controlled release, sustained release, or pulsatile release of the active agent.
- 20 23. The composition according to Claim 1 which results in immediate release of the active agent.
24. A process for making an electrospun pharmaceutical composition comprising a pharmaceutically acceptable active agent, and a pharmaceutically acceptable polymeric carrier, which process comprises
- 25 a) making a solution of the active agent, and pharmaceutically acceptable polymeric carrier with a pharmaceutically acceptable solvent; and  
b) electrospinning the solution of step (a) into a fiber.
- 30 25. The process according to Claim 24 wherein the solvent is water miscible.
26. The process according to Claim 24 wherein the solvent is water immiscible.
27. The composition according to Claim 24 wherein the solution is mixture of one or more solvents.
- 35

28. The process according to Claim 27 wherein the solvent is a mixture of water and a water miscible solvent.
29. The process according to Claim 24 wherein the polymeric carrier is  
5 poly(ethylene oxide), polyvinyl alcohol, polyvinyl pyrrolidone, hyaluronic acid, alginates, carragenen, carboxymethyl cellulose sodium, hydroxyethyl cellulose, hydroxypropylcellulose, hydroxypropylmethyl cellulose, hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, starch, hydroxyethyl starch, sodium starch glycolate, chitosan and its derivatives, albumen, gelatin, or collagen.
- 10 30. The process according to Claim 24 wherein the polymeric carrier is polyvinyl acetate, methyl cellulose, ethylcellulose, noncrystalline cellulose, polyacrylates and its derivatives, poly(alpha-hydroxy acids) and its copolymers such  
15 poly(caprolactone), poly(lactide-co-glycolide), poly(alpha-aminoacids) and its copolymers, poly(orthoesters), polyphosphazenes, poly(phosphoesters), or polyanhydrides.
31. The process according to Claim 24 wherein the active agent is an analgesic,  
20 anti-inflammatory agent, anthelmintic, anti-arrhythmic agent, an antibiotic, anticoagulant, antidepressant, antidiabetic agent, antiepileptic, antihistamine, antihypertensive agent, antimuscarinic agent, antimycobacterial agent, antineoplastic agent, immunosuppressant, antithyroid agent, antiviral agent, anxiolytic sedative, astringent, beta-adrenoceptor blocking agent, contrast media, corticosteroid, cough suppressant, diuretic, dopaminergic, homeostatic, immunological agent, lipid  
25 regulating agent, muscle relaxant, parasympathomimetic, parathyroid, calcitonin, prostaglandin, radio-pharmaceutical, sex hormone, steroid, anti-allergic agent, antihistaminic, stimulant, sympathomimetic, thyroid agent, vasodilator, PDE IV inhibitor, or a mixture thereof.
- 30 32. The composition according to Claim 24 wherein the active agent is an anti-inflammatory agent, a PDE IV inhibitor, nabumetone, aspirin, cis-4-Cyano-4-[3-cyclopentylloxy]-4-methoxyphenyl]-cyclohexanecarboxylic acid, or (S)-3-Hydroxy-2-phenyl-N-(1-phenylpropyl)-4-quinolinecarboxamide, Kytril, Zofran, Paroxetine, Ariflo, or Requip.
- 35 33. The product produced by the process according to Claim 24.

34. A process for making an electrospun pharmaceutical composition comprising a pharmaceutically acceptable active agent, and a pharmaceutically acceptable polymeric carrier, which process comprises

- 5           a) melting the active agent and polymeric carrier; and  
          b) electrospinning the melt of step (a) into a fiber.

35. The process according to Claim 34 wherein the polymeric carrier is poly(ethylene oxide), polyvinyl alcohol, polyvinyl pyrrolidone, hyaluronic acid, alginates, carragenen, carboxymethyl cellulose sodium, hydroxyethyl cellulose,  
10 hydroxypropylcellulose, hydroxypropylmethyl cellulose, hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, starch, hydroxyethyl starch, sodium starch glycolate, chitosan and its derivatives, albumen, gelatin, or collagen.

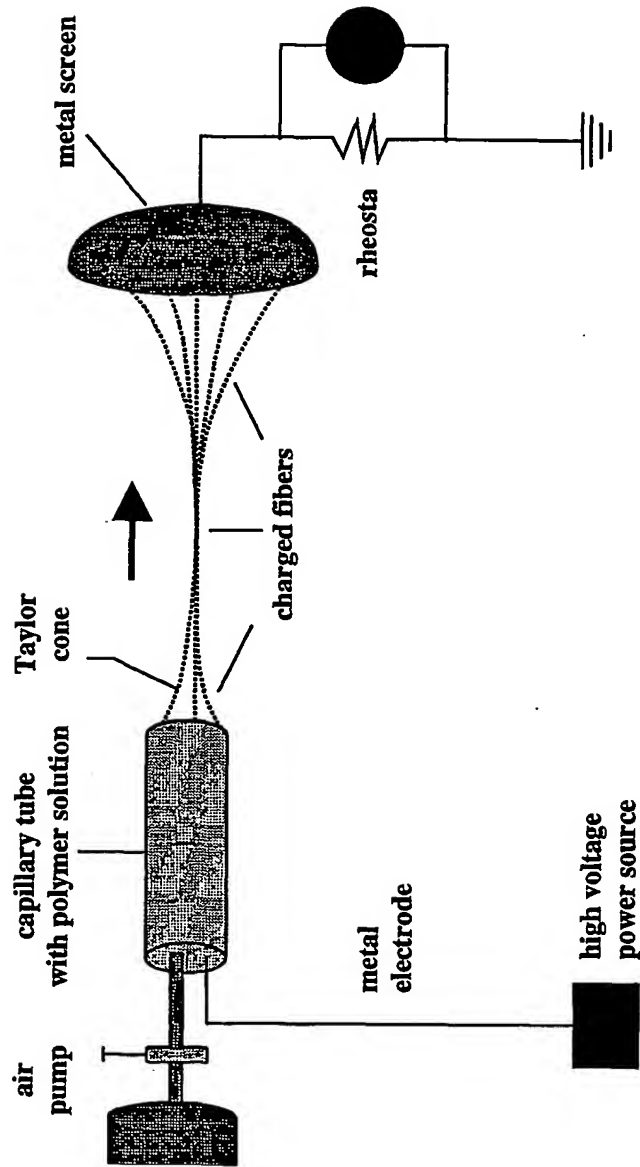
36. The process according to Claim 34 wherein the polymeric carrier is polyvinyl  
15 acetate, methyl cellulose, ethylcellulose, noncrystalline cellulose, polyacrylates and its derivatives, poly(alpha-hydroxy acids) and its copolymers such poly(caprolactone), poly(lactide-co-glycolide), poly(alpha-aminoacids) and its copolymers, poly(orthoesters), polyphosphazenes, poly(phosphoesters), or polyanhydrides.

20  
37. The process according to Claim 34 wherein the active agent is an analgesic, anti-inflammatory agent, anthelmintic, anti-arrhythmic agent, an antibiotic, anticoagulant, antidepressant, antidiabetic agent, antiepileptic, antihistamine, antihypertensive agent, antimuscarinic agent, antimycobacterial agent, antineoplastic  
25 agent, immunosuppressant, antithyroid agent, antiviral agent, anxiolytic sedative, astringent, beta-adrenoceptor blocking agent, contrast media, corticosteroid, cough suppressant, diuretic, dopaminergic, homeostatic, immunological agent, lipid regulating agent, muscle relaxant, parasympathomimetic, parathyroid, calcitonin, prostaglandin, radio-pharmaceutical, sex hormone, steroid, anti-allergic agent,  
30 antihistaminic, stimulant, sympathomimetic, thyroid agent, vasodilator, PDE IV inhibitor, or a mixture thereof.

38. The composition according to Claim 34 wherein the active agent is an anti-inflammatory agent, a PDE IV inhibitor, nabumetone, aspirin, cis-4-Cyano-4-[3-  
35 cyclopentylloxy]-4-methoxyphenyl]-cyclohexanecarboxylic acid, or (S)-3-Hydroxy-2-phenyl-N-(1-phenylpropyl)-4-quinolinecarboxamide, Kytril, Zofran, Paroxetine, Ariflo, or Requip.

39. The product produced by the process according to Claim 34.
40. Use of a composition according to Claim 1 for inhalation therapy.
- 5 41. Use of a composition according to Claim 1 for dispersion in an aqueous solution.
42. The composition according to Claim 1 wherein the active agent is
- 10 homogenously dispersed with the carrier in the fiber.



*Figure 1*

## Dissolution Data of Nabumetone Fibers

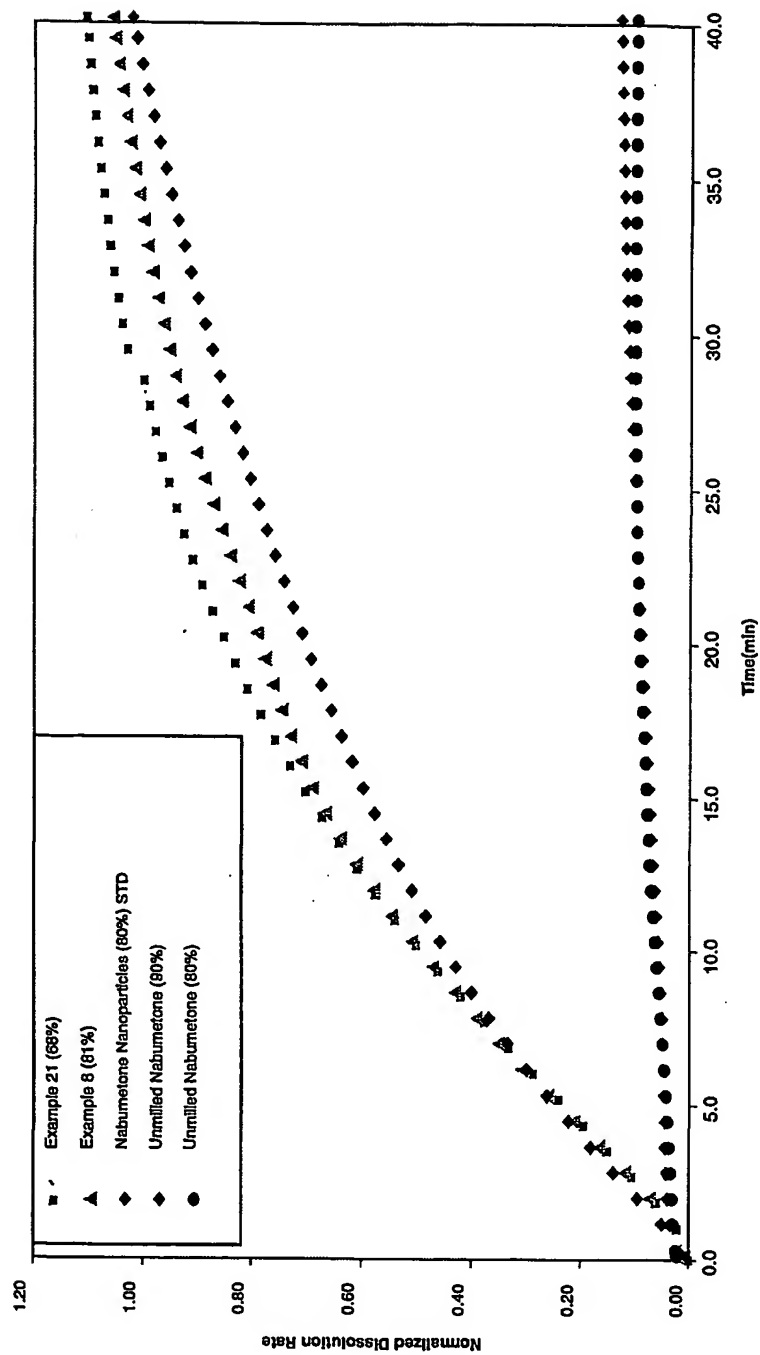


Figure 2

*Figure 3*

**SEM of PolyOx fibers containing 60 (w/w) % Nabumetone**



## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US01/02399

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) :A61K 9/14

US CL :424/486

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/486

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,567,439 A (MYERS et al) 22 October 1996, see abstract, column 4, lines 6-20, column 5, line 14 to column 6 and line 15, column 7, lines 8-35, column 9, lines 10-21, column 10, lines 5-34, column 11, line 37 to column 14 and line 59, column 15, lines 38-63, example and claim 8.	1, 3-39, 41 and 42
Y	US 5,736,152 A (DUNN) 07 April 1998, see column 2, line 42 to column 3 and line 13, column 4, line 63 to column 5 and line 8, column 6, lines 33-59, column 7, lines 9-50, column 9, line 11 to column 11 and line 67 and example 1.	1-42
Y	US 5,980,941 A (RAIDEN et al) 09 November 1999, see column 5, line 15 to column 12 and line 39.	1-42



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"G" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

07 APRIL 2001

Date of mailing of the international search report

07 MAY 2001

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

BLESSING FUBARA

Telephone No. (703) 308-0198

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/02399

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,869,098 A (MISRA et al) 09 February 1999, see column 2, lines 7-21, column 3, lines 49-64, column 5, lines 17-28, column 6, lines 16-55, column 8, line 32 to column 11 and line 25 and column 12, lines 12-37.	1-42